Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children

B. COOK, D. J. GRUBB, L. A. ALDRIDGE AND E. DOYLE

Summary

Sixty boys, aged 1–10 yr, undergoing orchidopexy were allocated randomly to receive one of three solutions for caudal extradural injection. Group A received 0.25 % bupivacaine 1 ml kg\(^{-1}\) with adrenaline 5\(\mu\)g ml\(^{-1}\) (1/200 000), group C received 0.25 % bupivacaine 1 ml kg\(^{-1}\) with clonidine 2\(\mu\)g kg\(^{-1}\) and group K received 0.25 % bupivacaine 1 ml kg\(^{-1}\) with ketamine 0.5 mg kg\(^{-1}\). Postoperative pain was assessed using a modified objective pain score and analgesia was administered if this score exceeded 4. The median duration of caudal analgesia was 12.5 h in group K compared with 5.8 h in group C \((P < 0.05)\) and 3.2 h in group A \((P < 0.01)\). There were no differences between the groups in the incidence of motor block, urinary retention or postoperative sedation. (Br. J. Anaesth. 1995; 75: 698–701)

Key words


The technique of caudal block with local anaesthetic provides analgesia during surgery which persists into the postoperative period and is one of the commonest analgesic techniques used in paediatric anaesthesia. A single caudal injection provides analgesia only for the duration of action of the local anaesthetic. Bupivacaine 2–2.5 mg kg\(^{-1}\) has a duration of action of 2–4 h. More than 60 % of children undergoing orchidopexy with this technique require further analgesia during the postoperative period [1].

Methods of prolonging the duration of caudal analgesia would clearly be useful. The addition of opioids to the local anaesthetic mixture is known to prolong the duration of caudal analgesia but the possibility of respiratory depression has limited the use of such mixtures. The commonest method is to add adrenaline 5\(\mu\)g ml\(^{-1}\) which increased the duration of caudal block in some studies but its effect tends to be relatively modest [2, 3].

Other alternative agents which may prolong the duration of caudal analgesia are ketamine and clonidine. Ketamine exerts its anaesthetic and analgesic actions by binding to a subset of glutamate receptors stimulated by the agonist N-methyl D-aspartate (NMDA). These are found throughout the central nervous system, including the lumbar spinal cord. In addition to a general analgesic effect produced by systemic administration, ketamine exerts profound analgesic actions at the spinal cord level in animal preparations [4, 5]. In clinical practice ketamine injection into the lumbar extradural space after abdominal surgery has been shown to have a potent analgesic effect [6, 7]. In children, a mixture of 0.25 % bupivacaine 1 ml kg\(^{-1}\) and ketamine 0.5 mg kg\(^{-1}\) has been shown to improve the duration and quality of analgesia provided by caudal block after herniotomy [8].

Extradural or intrathecal clonidine produces analgesia and has been shown to be effective alone [9–11] and when combined with bupivacaine for extradural use [12]. A mixture of 0.25 % bupivacaine 1 ml kg\(^{-1}\) and clonidine 2\(\mu\)g kg\(^{-1}\) has been shown to produce a longer duration of caudal analgesia in children after lower body surgery than bupivacaine alone [13] while a mixture of 0.25 % bupivacaine and clonidine 1\(\mu\)g kg\(^{-1}\) was superior to bupivacaine with adrenaline 1/200 000 [14].

This study was designed to compare the addition of ketamine, clonidine and adrenaline on the duration of caudal block produced by 0.25 % bupivacaine 1 ml kg\(^{-1}\).

Patients and methods

The study was approved by the local Ethics Committee and written informed parental consent was obtained for each subject. We studied 60 boys, aged 1–10 yr, undergoing unilateral orchidopexy as day cases. Exclusion criteria included contraindications to caudal block and parental inability or unwillingness to perform objective pain assessments. At the time of recruitment, parents were instructed in the use of the modified objective pain score (OPS) for assessment of postoperative pain and requirement for analgesia. This is an observational pain scoring...
system using five criteria: crying, agitation, movement, posture and localization of pain. Each criterion scores 0–2 to give a total score of 0–10 [1, 15].

Premedication was not used and EMLA cream was applied to the dorsum of the hand at least 1 h before operation. Anaesthesia was induced with propofol 3–4 mg kg\(^{-1}\) followed by placement of a laryngeal mask airway of appropriate size. Anaesthesia was maintained with 0.5 %–2 % halothane and 70 % nitrous oxide in oxygen.

After induction of anaesthesia, patients were placed in the lateral position and a caudal injection performed using an aseptic technique by a consultant anaesthetist. Patients were allocated randomly to one of three groups of 20 using a computer-generated list. Group A received a caudal injection of 0.25 % bupivacaine 1 ml kg\(^{-1}\) with adrenaline 1/200 000 (5 μg ml\(^{-1}\)), group C received 0.25 % bupivacaine 1 ml kg\(^{-1}\) with clonidine 2 μg kg\(^{-1}\) and group K received 0.25 % bupivacaine 1 ml kg\(^{-1}\) with 0.5 mg kg\(^{-1}\) of preservative-free ketamine 10 mg ml\(^{-1}\). The maximum volume injected was 20 ml.

Anaesthetic agents were discontinued at completion of skin closure and patients moved to the recovery area. The time from discontinuation of anaesthesia to spontaneous eye opening was noted. Before discharge, analgesia was requested by the parents (who were unaware of the mixture used for caudal injection) when their estimate of the OPS was ≥ 4. Paracetamol 10 mg kg\(^{-1}\) orally every 4 h was given as required. The duration of motor block was assessed by noting when patients began to move their legs. The time of first micturition was also noted. Assessments of sedation were made at 1 and 4 h after operation using an objective score based on eye opening (eyes open spontaneously = 0, eyes open in response to verbal stimulation = 1, eyes open in response to physical stimulation = 2).

After discharge parents were asked to assess the child regularly and to give analgesia (paracetamol 15 mg kg\(^{-1}\) orally) if OPS was ≥ 4. Parents were contacted by telephone the day after surgery to determine the requirement for analgesia after discharge from hospital. The total requirement for analgesia in the first 24 h after operation was noted.

Statistical analysis was performed using Student’s \(t\) test for parametric data and the Mann–Whitney \(U\) test and chi-square test for non-parametric data.

**Results**

The three groups were similar in characteristics and duration of surgery (table 1).

The median time to first analgesia was significantly longer in group K (12.5 h) than in group A (3.2 h) \((P < 0.01)\) and group C (5.8 h) \((P < 0.05)\). The difference in median time to first analgesia in group C was significantly longer than in group A \((P < 0.05)\) (fig. 1).

The number of doses of postoperative analgesics required was significantly greater in group A compared with groups C \((P < 0.05)\) and K \((P < 0.01)\). Fourteen subjects in group K required none or one dose only of postoperative analgesia compared with 10 in group C \((P < 0.05)\) and one in group A \((P < 0.01)\) (table 2).

There were no significant differences between the groups in the median time taken to spontaneous eye opening after cessation of anaesthesia (group A 20 (range 5–44) min, group C 21 (8–42) min, group K 24 (10–40) min). There were no significant differences in median sedation scores in the groups at 4 h after operation (group A 0 (range 0–1), group C 0 (0–1), group K 0 (0–1)).

The time to first micturition (group A 4.75 (1.75–18) h, group C 7.0 (2–20) h, group K 5.5 (1–22) h) and spontaneous leg movements (group A 3.5 (1–12) h, group C 3.5 (1.5–12) h, group K 3.0 (1–13) h) were similar in the three groups.

**Discussion**

We have confirmed the findings of previous workers that the addition of ketamine 0.5 mg kg\(^{-1}\) or clonidine 2 μg kg\(^{-1}\) to 0.25 % bupivacaine prolongs the duration of caudal block more than adrenaline 1/200 000 [8, 13, 14]. This is the first study to compare the effects of ketamine and clonidine on the duration of caudal block and our results indicated that ketamine had the more pronounced action. Our findings for both ketamine and clonidine were less striking than those of previous studies. The mean duration of

---

**Table 1** Patient data for subjects in groups A, C and K (mean (SD or range))

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (kg)</th>
<th>Age (months)</th>
<th>Duration of surgery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>22.2 (9.8)</td>
<td>61.1 (16–120)</td>
<td>26 (15–41)</td>
</tr>
<tr>
<td>Group C</td>
<td>20.1 (8.8)</td>
<td>60.3 (15–108)</td>
<td>23 (12–42)</td>
</tr>
<tr>
<td>Group K</td>
<td>23.1 (7.1)</td>
<td>72.4 (18–108)</td>
<td>22 (13–40)</td>
</tr>
</tbody>
</table>

---

**Table 2** Requirement for supplementary postoperative doses of paracetamol in groups A, C and K.

<table>
<thead>
<tr>
<th>No. of doses given</th>
<th>Group A</th>
<th>Group C</th>
<th>Group K</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
caudal block produced by 0.25% bupivacaine 1 ml kg⁻¹ with clonidine 2 μg kg⁻¹ was 9.8 h compared with 5.2 h for plain 0.25% bupivacaine 1 ml kg⁻¹ [13]. This study used patients undergoing orthopaedic surgery premedicated with trimepazine, morphine and atropine. These drugs may have had a synergistic effect with bupivacaine and clonidine to prolong the duration of postoperative analgesia. When clonidine 1 μg kg⁻¹ was added to 0.25% bupivacaine 1 ml kg⁻¹, the mean duration of postoperative caudal analgesia was 16 h [14]. This study was performed in a group of children undergoing diverse procedures and premedicated with diazepam 0.3 mg kg⁻¹ or, in some patients, hydroxyzine 1 mg kg⁻¹. An investigation of the effect of adding ketamine 0.5 mg kg⁻¹ to 0.25% bupivacaine 1 ml kg⁻¹ in children undergoing inguinal herniotomy found that 93% of patients required no further postoperative analgesia [8]. The more modest effect in our study may be because the operation we studied (orchidopexy) is more extensive and painful than inguinal herniotomy.

The use of parents to assess pain and decide when to give analgesia has not been reported previously but may be expected to be a valid method if an objective method of assessing pain is used with defined criteria for the administration of analgesia. Any parental inconsistencies in using the score or deciding to medicate children are likely to have been random and to have affected the three groups equally. It may be that parents are the best people to assess pain or distress in a child as they know the child best.

We found no additional problems with prolonged motor block, as shown by differences in leg weakness or urinary retention in the clonidine or ketamine groups. Prolonged postoperative sedation in patients given clonidine has been reported [13]. However, these patients were premedicated with trimeprazine, morphine and atropine and the precise criteria for defining excessive sedation were not given. The duration and degree of postoperative sedation in our study were similar in the three groups. Assessment of the incidence and severity of postoperative nausea and vomiting was not included in this study and it may be criticized because of this. Postoperative nausea and vomiting are common reasons for delayed discharge after day-case surgery and any analgesic intervention which increases the incidence or severity of these symptoms is unlikely to become popular even if it is effective.

The doses of clonidine and ketamine used in this study were chosen because they have been used safely in previous studies in children and adults. The addition of clonidine 1 μg kg⁻¹ to 0.25% bupivacaine produced significant prolongation of caudal block in children undergoing various urological procedures [14] and this may be as effective as 2 μg kg⁻¹. There are no dose finding studies for these drugs used extradurally in children and there is a need to identify the optimal doses of these drugs for use as adjuvants to local anaesthetics for caudal block.

The use of ketamine by the extradural route may raise reservations about potential toxicity. No major sequelae have been reported after the use of extradural 1% ketamine in human studies. Animal studies have demonstrated the safety of intrathecal 1% ketamine after a single dose [16–18] and after multiple (14) doses without preservative [19]. Ketamine 5% produced local neuronal damage after subarachnoid administration in rats [20]. The preservative benzethonium chloride has been shown to be non-toxic in primates [16, 17]. Local nerve root damage in these studies was considered to be caused by traumatic lumbar puncture. One study [21] has claimed to show a definite neurotoxic effect of 1% ketamine. In this study the drug was administered into the intracisternal subarachnoid space of rabbits through the atlanto-occipital membrane. The investigators found no differences on light microscopy between the spinal cords of animals treated with saline or 1% lignocaine and those treated with ketamine. As a test of the integrity of the blood–brain barrier, Evans blue was also injected intracisternally and subsequently sought out with spinal blood vessels using fluorescence microscopy. The dye passed from cerebrospinal fluid to plasma at a more marked degree in two of 10 rabbits treated with ketamine than in those treated with saline or lignocaine. The same workers subsequently demonstrated that the preservative used in their previous study, chlorobutanol (not used in the UK), caused neurotoxicity when administered intrathecally while 1% ketamine and the isomer 1% d-ketamine without preservative did not cause neurotoxicity [18]. A study in rats which used high doses of intrathecal ketamine (1.6 mg kg⁻¹) had three deaths (in 33 animals) during injection. In these animals, death was presumed to be caused by supraspinal spread of ketamine during injection through the atlanto-occipital membrane [22].

References


